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WRITER'S DIRECT NUMBER:

February 1, 1991

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Re: U.S. Utility Patent Application
Appln. No.: 07/460,852; filed Feb. 21, 1990
For: TREATMENT OF AUTOIMMUNE DISEASES BY
ORAL ADMINISTRATION AUTOANTIGENS
Inventors: Weiner, H. *et al.*
Our Ref: 0627.1220004

Mohamed

Sir:

The following documents are submitted herewith for appropriate action by the U.S. Patent and Trademark Office:

1) Information Disclosure Statement;
2) A list of the cited references on Form PTO-1449;
3) A copy of each of the cited references; and
4) Post card.

It is respectfully requested that the attached postpaid post card be stamped with the date of filing of these documents, and that it be returned as soon as possible. A duplicate copy of this letter is attached.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX

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MAC/ARB:mbm
Encls.

F.17-BW122.MBM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
HOWARD WEINER *et al.*	:	Art Unit: 186
Appl. No.: 07/460,852	:	
Filed: February 21, 1990	:	
For: TREATMENT OF AUTOIMMUNE DISEASES BY ORAL ADMINISTRATION AUTOANTIGENS	:	Atty Docket: 0627.1220004

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

Submitted herewith on Form PTO-1449 is a listing of documents known to the Applicants and/or their agent in compliance with the requirements of 37 C.F.R. § 1.56. Copies of the documents are also being submitted.

Applicants do not waive any rights to appropriate action to establish patentability over any of the listed documents should they be applied as references against the claims of the present application.

REMARKS

Documents are arranged in the order that they appear in the specification, with documents not cited in the application listed at the end.

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Reference AR1, Wells, referred to on page 1 of the specification, discloses a method of inducing immunologic tolerance by the oral administration of an antigen to prevent autoimmune responses.

Reference AS1, Ngan, referred to on page 2 of the application, reports that a single oral dose of ovalbumin resulted in inhibition of IgE formation in mice subsequently immunized with ovalbumin, and that repeated feeding of ovalbumin induced the formation of detectable suppressor cells in the Peyer's patch and spleen.

Reference AT1, Gautam, referred to on page 1 of the application, reports that the oral administration of the hapten trinitrochlorobenzine (TCNB) suppresses development of contact sensitivity to attempted epicutaneous sensitization with this same hapten. This suppression was found to be hapten specific and was transferred to normal animals with lymphoid cells from fed mice.

Reference AR2, Titus, referred to on page 2 of the application, discloses that intragastric exposure of mice to T-dependent antigens ovalbumin, bovine serum albumin, and human gamma globulin severely compromised the ability to respond to a subsequent challenge with the homologous antigen.

Reference AS2, Nagler-Anderson, referred to on pages 2 and 4 of the application, discloses the suppression of type II collagen-induced arthritis by intragastric administration of soluble type II collagen.

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Reference AT2, Swierkosz, referred to on page 2 of the application, discloses the requirements for the induction of immunoregulatory suppressor cells in experimental allergic encephalomyelitis (EAE) in Lewis rats.

Reference AR3, Lando *et al.*, referred to on page 2 of the application, discloses the induction of experimental allergic encephalomyelitis in genetically resistant strains of mice. This reference discloses further that suppressor T cells account for the unresponsiveness to EAE that is exhibited by some mouse strains.

Reference AS3, Lando *et al.*, referred to on page 2 of the application, discloses that suppressor cells that mediate unresponsiveness to EAE also regulate the cellular immune response to the basic encephalitogenic protein in a specific manner.

Reference AT3, Sriram *et al.*, referred to on page 2 of the application, discloses that administration of myelin basic protein-coupled spleen cells prevents EAE.

Reference AR4, Alvord *et al.*, referred to on page 2 of the application, discloses the suppression of EAE in monkeys by the parenteral administration of myelin basic protein (MBP) when administered together with a non-specific adjunctive factor, e.g., an antibiotic or a steroid.

Reference AS4, Alvord *et al.*, referred to on page 2 of the application, discloses the treatment of EAE in monkeys with MBP and an adjunct.

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Reference AT4, Alvord *et al.*, referred to on page 2 of the application, discloses degradation of MBP by cerebrospinal fluid.

Reference AR5, Traugott *et al.*, referred to on page 3 of the application, discloses the treatment of guinea pigs with chronic relapsing EAE with injections containing either MBP alone or MBP in incomplete Freund's adjuvant, or MBP in combination with a lipid hapten of myelin, galactocerebroside (GC) in incomplete Freund's adjuvant.

Reference AS5, Raine *et al.*, referred to on page 3 of the application, discloses the treatment of chronic relapsing EAE with MBP alone in incomplete Freund's adjuvant or in combination with a lipid hapten, galactocerebroside (GC) in incomplete Freund's adjuvant.

Reference AT5, McKenna *et al.*, referred to on page 3 of the application, discloses the suppression of EAE in Lewis rats by treatment with MBP cell conjugates.

Reference AR6, Strejan *et al.*, referred to on page 3 of the application, discloses the suppression of EAE in Lewis rats treated with MBP-liposome complexes.

Reference AS6, McKenna *et al.*, referred to on page 3 of the application, reports on studies of the mechanism of EAE induced by MBP-cell conjugates.

Reference AT6, Burns *et al.*, referred to on page 3 of the application, reports on human cellular immune response to copolymer I and MBP.

Reference AR7, Belik *et al.*, referred to on page 3 of the application, reports on the treatment of guinea pigs with EAE by

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alkaline protein of myelin and by synthetic encephalitogenic peptide.

Reference AS7, Braley-Mullen *et al.*, referred to on page 4 of the application, discloses the suppression of experimental autoimmune thyroiditis (EAT) in guinea pigs by pretreatment with thyroglobulin in incomplete Freund's adjuvant.

Reference AT7, Kardys *et al.*, referred to on page 21 of the application, discloses a single amino acid substitution in the major encephalitogenic sequence in bovine myelin basic protein. This mutated peptide failed to induce clinical or histological signs of EAE but conferred resistance to EAE in Lewis rats.

Reference AR8, Holoshitz *et al.*, referred to on page 21 of the application, discloses T lymphocyte lines that are effective in mediating or preventing EAE. The lines are also reactive with antigenic determinants on the basic myelin protein other than the major encephalitogenic peptide determinant.

Reference AS8, Mokhtarian *et al.*, referred to on page 23 of the application, reports that the adoptive transfer of MBP-sensitized T cells produces chronic relapsing demyelating disease in mice.

Reference AT8, McDermott *et al.*, reports on antigen-induced suppression of experimental allergic neuritis (EAN) in the guinea pig. Treatment of guinea pigs suffering from a fatal form of EAN using P_2 basic protein of peripheral nervous system myelin reduced the clinical severity, the overall mortality, and the incidence of respiratory problems.

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Reference AR9, Raziuddin *et al.*, discloses the immunosuppression of EAE. In this reference, the authors examined a suppressor mechanism expressed in the responses of rat lymph node cells to MBP, and bacterial lipopolysaccharides (LPS), from MBP-LPS immunized rats that became unresponsive to induction of EAE.

Reference AS9, Alvord *et al.*, discloses the inhibition of experimental allergic encephalomyelitis (EAE) by the administration of either whole central nervous system or basic protein central nervous system extracts. The route of administration was by intracutaneous or subcutaneous injection. Administration of the extracts was before and/or following the induction of EAE.

Reference AT9, Eylar, discloses suppression of EAE in Rhesus monkeys following the intramuscular injection of human myelin basic protein. The injection was given following onset of the disease. The results show that only three of the 16 animals treated with the protein died, whereas all control animals died.

Reference AR10, Schoen *et al.*, discloses a method for suppressing collagen-induced arthritis (CIA) in rats. Collagen coupled to spleen cells was injected into rats. Neither collagen alone nor cells alone was effective in suppressing CIA. The effect appeared to be antigen-specific.

Reference AS10, Eylar, discusses EAE as an animal model of human autoimmune disease. It also discusses subregions of myelin basic protein from various species, which subregions are capable of inducing EAE in several species. It also cites studies in

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which myelin basic protein injection is shown to prevent the induction of EAE.

Reference AT10, Bitar *et al.*, discloses studies in which myelin basic protein was orally administered to animals prior to the induction of EAE. Lymphocyte proliferation response in animals fed MBP was compared with control animals that were either fed ovalbumin or were fed MBP intragastrically. Feeding the animals MBP resulted in a marked inhibition of the proliferative response. In comparisons of the onset and severity of EAE among the animals that were fed MBP, 52% showed no clinical manifestation of EAE. In contrast, EAE was induced in 97% of the vehicle-fed animals. In the animals fed myelin basic protein, the histopathological manifestations were also diminished.

Reference AR11, Whitacre *et al.*, discloses that 58% of the rats that received an oral dose of 20 mg of guinea pig myelin basic protein, given in multiple doses, were protected from subsequent development of EAE. The abstract also discloses that oral administration of myelin basic protein may be of value in establishing a therapeutic protocol for multiple sclerosis.

Reference AS11, Higgins *et al.* discloses a regimen of oral administration of myelin basic protein that prevents the development of EAE. No animals fed MBP developed EAE while 80% of control animals developed the disease.

Reference AT11, Whitacre *et al.*, discloses a title of a workshop given in Kyoto, Japan on EAE induction and oral administration of myelin basic protein.

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Reference AR12, Higgins *et al.*, discloses a procedure for suppressing the development of EAE by the oral administration of myelin basic protein and myelin basic protein fragments. The disease was suppressed by whole MBP and by encephalitogenic and non-encephalitogenic peptide fragments. Animals were protected when fed either before or after induction of the disease.

Reference AS12, Gonsette *et al.*, discloses the effects of injection of myelin basic proteins in multiple sclerosis patients. Weekly injections were given to patients for 3 to 11 months with a mean time of 7.5 months. A two-year followup was done to measure annual relapse rates. In this study, the injections did not produce amelioration or stabilization of the disease.

Reference AT12, Myers *et al.*, discloses the isolation of a subset of T cells that can confer resistance to collagen-induced arthritis when the cells are administered to naive animals prior to induction of the disease. T cells conferring resistance are derived from the spleens of animals receiving IV intravenous injection of type 2 collagen. The depletion of $CD4^+$ cells from the splenic cell population prior to transfer abrogates the effect.

Reference AR13, Myers *et al.*, discloses specific peptide fragments from type 2 collagen that are able to suppress collagen-induced arthritis in animals. The administration of these peptide fragments induces tolerance to the antigenic collagen protein in the animal. Peptides were injected intravenously before immunization with native type 2 collagen.

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Reference AS13, Lider *et al.*, discloses that in animals that have been orally tolerized with myelin basic protein, populations of cells are induced that transfer resistance to EAE in naive syngeneic recipients. Adoptive transfer of disease suppression was dependent upon the presence of $CD8^+$ T cells in the cell populations that were removed from the orally tolerized animals. T cells from animals fed myelin basic protein were also found to suppress the *in vitro* proliferation of T cells. $CD8^+$ and $CD3^+$ cells were required to suppress the *in vitro* proliferation response.

Reference AT13, Higgins *et al.*, discloses the effects of EAE induction in Lewis rats fed myelin basic protein and myelin basic protein fragments. The clinical and histologic manifestations of EAE were suppressed in the rats by the oral administration of MBP and its fragments. It was also shown that suppression was induced by non-encephalitogenic fragments more effectively than it was induced by encephalitogenic fragments of MBP.

Reference AR14, Campbell *et al.*, discloses a double-blind clinical trial which tested the effects of injection of human myelin basic protein on 64 multiple sclerosis patients. These studies were designed in order to assess the feasibility of injecting human myelin basic protein into human patients, particularly to assess toxic side effects.

Reference AS14, Trentham *et al.*, discloses studies *in vitro* and *in vivo* that show that there is a collagen-sensitive population of lymphocytes in rats with adjuvant arthritis. Studies also show that arthritic but not normal rats contain

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antibodies that react with collagen. These studies suggest that autoimmunity to collagen may be important in adjuvant arthritis.

Reference AT14, Thompson *et al.*, discloses studies in which the onset of collagen-induced arthritis was delayed and severity of the condition reduced when rats were dosed pergastrically with type 2 collagen. The administration was done prior to the arthritogenic challenge.

Reference AR15, Mowat, reviews the regulation of the immune response to dietary protein antigens. It shows that in general, the result of ingestion of a protein antigen by the oral route is the induction of specific immunological tolerance. It discusses several of the immunoregulation mechanisms that may be involved in the induction of oral tolerance.

This statement should not be construed as a representation that more material information does not exist or that an exhaustive search of the relevant art has been made.

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Consideration of the cited documents and making the same of record in the prosecution of the above-noted application are respectfully requested.

Respectfully submitted,

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